Amendment 1

Applicants amend claims 1, 17, 20, 23 and 31 to specify that the recited purified osteogenic protein is "not associated with other osteogenic proteins with which it is normally associated *in vivo*." Support for this amendment appears in the specification at p. 40, lines 7-11 and 19-22.[2] This amendment is made in response to the Examiner's comments in the Office Action at p. 3, lines 8-11; p. 6, lines 2-5; p. 7, lines 7-10; and p. 9, lines 2-5. In those portions of the Office Action, the Examiner states that applicants relied on a certain feature of the invention -- the purified osteogenic protein is not associated with other osteogenic proteins with which it is normally associated *in vivo* -- to overcome the prior art rejections, but applicants failed to recite this feature in the rejected claims.

During the June 27 interview, the undersigned proposed this amendment. The Examiner stated that this amendment would overcome the rejections based on Sato. But he was concerned that the amendment may necessitate new grounds of rejection since

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2 In the Advisory Action, the Examiner stated that he could not find support for this amendment in these passages. Applicants submit that these passages inherently, thought not necessarily literally, support the amendment. It is well settled in U.S. patent law that support for a claim in the specification need not be verbatim. In these passages, the specification teaches that BMPs useful in this invention can be produced by recombinant techniques or other synthetic techniques (e.g., chemical synthesis). The BMPs so produced inherently do not associate with other osteogenic proteins with which it is normally associated *in vivo*. For instance, a cDNA encoding OP-1 can be expressed in "prokaryotic [e.g., *E. coli*] or eukaryotic cells [e.g., CHO, COS or BSC cells], purified, cleaved, refolded, and dimerized to form morphogenically active compositions." (p. 40, lines 20-24). The OP-1 so produced is in a purified form, not associated with any other BMPs.

purified OP-1 was known in the art.[3] Applicants believe that Amendment 3 discussed below addresses this concern.

Amendment 2

Applicants further amend claim 1 to define that the recited matrix "does not comprise a synthetic polymer or demineralized bone." This amendment was suggested by the Examiner during the June 27 interview to clarify the meaning of "a matrix other than a synthetic polymer or demineralized bone." The amendment addresses issues raised in the Office Action at p. 4, lines 4-5, and 11-12; p. 5, lines 2-3; and p. 10, lines 9-12.[4]

Amendment 3

To expedite prosecution, applicants also further amend claim 1 to specify that the binding agent is "selected from the group consisting of mannitol, dextran, cellulose, white petrolatum, and derivatives thereof." This amendment incorporates certain limitations of claim 10 into claim 1. Support for this amendment appears in claim 10 as originally filed, and in the specification at p. 25, 1st ¶.

Amendment 4

Applicants have also amended claims 2 and 3 to replace the term "conservative amino acid sequence variants" with "variants [ ] having conservative amino acid substitutions." Support for this amendment appears in the specification at p. 23, lines

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3 See also the Interview Summary mailed June 29, 2000.

4 The Advisory Action acknowledges that this amendment would overcome the indefiniteness rejection of claims 1-6, 9-16, 32, 33, 35 and 36.

[redacted]

8-15 and p. 27, line 12 through p. 28, line 3. During the June 27 interview, the Examiner agreed that this amendment would overcome the indefiniteness rejection raised at p. 2, ¶ 4 of the Office Action.[5]

Amendment 5

Applicants delete claim 10 without prejudice.

Amendment 6

Applicants amend claims 32 and 35 to make it clearer that the "osteogenic protein," "matrix" and "binding agent" recited therein refer to those recited in base claim 1 and hence incorporate all the limitations of claim 1.

Reconsideration of the application is respectfully requested in view of the above proposed amendments and the following remarks.

Rejection Under 35 U.S.C. § 112, 2nd ¶

I

Claims 2 and 3 remain rejected as allegedly indefinite. Specifically, the Examiner states that the recited term "conservative amino acid sequence variants" is unclear and applicants' argument in the January 24, 1999 Response ("previous Response") is unpersuasive because the feature on which applicants relied, i.e., conservative amino acid substitution, is not recited in the rejected claims. Office Action, p. 2, ¶ 4.

In light of the Examiner's comments, applicants have amended claims 2 and

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5 In the Advisory Action, the Examiner also acknowledges that this amendment would overcome the indefiniteness rejection of claims 2 and 3.

3 to replace the allegedly unclear term with "conservative amino acid substitutions."

II

The Examiner has raised a new rejection concerning claims 1-6, 9-16, 32, 33, 35, and 36. Specifically, the Examiner states that it is not clear whether "the claimed device comprises a matrix that is not a synthetic polymer and that is not demineralized bone, or if the device comprises a matrix other than a synthetic polymer or the device comprises demineralized bone." Office Action, p. 10, ¶ 13.

Applicants respectfully point out that the first interpretation is correct. For clarification, applicants amend base claim 1 as discussed above, that is, to state that the matrix "does not comprise a synthetic polymer or demineralized bone" (Amendment 2, *supra*).

Rejection Under 35 U.S.C. § 102(b)

Claims 1-5, 7, 15, 20, 22, and 23 remain rejected as allegedly anticipated by Sato. Specifically, the Examiner states that applicants' arguments in their previous Response are not persuasive, because the feature on which applicants relied -- the purified protein is not associated with other osteogenic proteins with which it is normally associated -- is not recited in the rejected claims. Office Action, pp. 3, 6, 7, and 9.

In light of the Examiner's comments, applicants have amended claims 1, 20, and 23 to recite this feature (Amendment 1, *supra*). The remaining rejected claims depend either from claim 1 or from claim 20. Applicants believe that this amendment would

overcome the instant rejection.

Rejection Under 35 U.S.C. § 102(e)

Claims 1-5, 7, 8-12, 15 and 16 remain rejected as allegedly anticipated by Kuberasampath (United States Patent 5,645,591). Specifically, the Examiner states that applicants' arguments in their previous Response are not persuasive, because the matrix used in the claimed device "does not exclude a matrix that is a synthetic polymer." Office Action, p. 4.

The Examiner appears to have misunderstood the claims. Base claim1 recites "a matrix other than a synthetic polymer . . ." As such, all of the rejected claims do exclude a matrix that is a synthetic polymer.

For clarification, applicants have amended claim 1 to state that the matrix "does not comprise a synthetic polymer or demineralized bone" (Amendment 2, *supra*). This language was suggested by the Examiner during the June 27 interview. Applicants believe that this amendment would overcome the instant rejection.

Rejection Under 35 U.S.C. § 103(a)

I

Claims 1, 32, 33, 35 and 36 remain rejected as allegedly obvious over Kuberasampath. Specifically the Examiner states that the claimed device does not exclude a matrix that is a synthetic polymer. Office Action, p. 4, ¶ 7.

[redacted]

As discussed above, the rejected claims do exclude the use of a synthetic polymer as a matrix. This exclusion is made even more explicit by proposed Amendments 2 and 6, *supra*. As such, this rejection should be withdrawn.

II

Claims 1, 13 and 31 remain rejected as allegedly obvious over Kuberasampath in view of Wozney (WO 95/24210) and Ammann (WO 94/15653). Office Action, p.4, ¶ 8.

(1) Claims 1 and 13

Regarding these two claims, the Examiner argues that the claimed device does not exclude the use of a synthetic polymer as a matrix. As discussed above, this is not the case, especially in light of Amendment 2. Thus, the rejection to these two claims should be withdrawn.

(2) Claim 31

With regard to claim 31, the Examiner dismisses the unexpected results pointed to by applicants in their previous Response. Specifically, the Examiner states that Ammann's "smooth, moldable putty or paste" would have led a person of ordinary skill in the art to reasonably believe that the implant would form "a more continuous layer with irregular host bone defect sites and more frequent new bone would be formed that is continuous with the host bone" (Office Action, p. 5, lines 9-11).

Applicants respectfully disagree. Ammann, like Kuberasampath and Wozney, fails to teach or even suggest the combined use of the particular ingredients

recited in claim 31, i.e., OP-1, collagen matrix, and CMC. In fact, this particular combination was taught away by the prior art.

At the time of the invention, it was known in the art that CMC and collagen are incompatible in pharmaceutical formulations. See the section entitled **Incompatibilities** in the *Handbook of Pharmaceutical Excipients*, 2nd Ed., Wade and Weller, Eds., The Pharmaceutical Press, London (1994), p. 7 (Exhibit 1).[6] Based on this teaching, a person of ordinary skill in the art would not have wanted to combine CMC and collagen in formulating a device for bone and cartilage repair. And applicants' successful use of a CMC/collagen device would not have been expected.[7]

Further, the Examiner fails to address applicants' argument in their previous Response that none of Kuberasampath, Wozney and Ammann provides any motivation for the very combination of OP-1, collagen matrix, and CMC, the three ingredients recited in claim 31. MPEP 706.02(j) promulgates three criteria for establishing a *prima facie* case of obviousness. The first criterion is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of

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6 This Section of the *Handbook* states: "Carboxymethylcellulose sodium additionally forms a complex with collagen and is capable of precipitating certain positively charged proteins."

7 The Examiner also states that applicants' unexpected results were obtained with low doses of OP-1, but claim 31 is not limited to low doses of OP-1. Applicants' working examples did demonstrate the synergistic effect of CMC/collagen with low doses of OP-1. However, this does not mean that the advantage of CMC/collagen only exists where a low dose of OP-1 is used.

ordinary skill in the art, to modify the reference or to combine reference teachings. The instant rejection does not meet this criterion.

III

Claims 1 and 13 remain rejected as allegedly obvious over Sato in view of Wozney. The Examiner states that applicants' arguments in their previous Response are not persuasive because the feature relied upon (i.e., the meaning of "purified") is not recited in the claims. Office Action, p. 5, ¶ 9.

In light of this comment, applicants have amendrf claim 1 to recite this feature (Amendment 1, *supra*). In addition, in the interest of moving this case forward, applicants have excluded fibrin glue from claim 1 as a binding agent, without further addressing the merit of the Examiner's rejection (Amendment 3, *supra*). Claim 1 now requires that the binding agent is mannitol, dextran, cellulose, white petrolatum, or a derivative thereof.

Sato does not teach or suggest the use of any of these binding agents. Wozney, on the other hand, does not suggest the use of a sequestering agent in conjunction with a matrix that is not a synthetic polymer. And neither reference provides any motivation to arrive at the combined use of (1) a matrix that does not comprise a synthetic polymer or demineralized bone and (2) cellulose, dextran, white petrolatum or a derivative thereof.

As a result, claim 1 as amended would not have been rendered obvious by Sato and Wozney. Claim 13, dependent from claim 1, would have been be non-obvious

for the same reasons.[8]

IV

Claims 1, 13, 17-25 and 31 remain rejected as allegedly obvious over Sato in view of Wozney, Doll, Cook, Nunez (WO 94/20133), Ammann, Alberts, and Reddi. Office Action, p. 6, ¶ 10. The Examiner states that applicants' previous arguments are not persuasive because the feature relied upon (the meaning of "purified") is not recited in the rejected claims. In view of this comment, applicants have amended independent claims 1, 17, 20, 23 and 31 to recite this feature (Amendment 1, *supra*).

Sato and Wozney have been discussed above in light of Amendments 1 and 3. Applicants address below the Examiner's arguments regarding the remaining references. See Office Action at p. 7, line 15 through p. 8, line 14.

Doll

The Examiner argues that Doll "teaches that collagen matrix may provide a more permissive surface for cell attachment than HA . . ." Office Action, p. 7, lines 15-18. However, Doll discloses that satisfactory bone regeneration was achieved with osteogenin and insoluble collagen without the use of any binding agent. Doll does not identify any problem associated with the lack of a binding agent. Therefore, this reference provides no

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8 With respect to claim 13, the Examiner also points out that Wozney's autologous blood is fibrin glue. Office Action, p. 6, lines 10-11. This is not true. It is well understood in the art that fibrin glue refers to a man-made composition formed by admixing fibrinogen, Factor XIII and thrombin. See, e.g., Sato, p. 254, right column, penultimate full paragraph. It does not contain blood cells or most of the other plasma proteins found in blood clots.

motivation for the use of a binding agent, such as mannitol, dextran, cellulose, white petrolatum or a derivative thereof, in conjunction with its collagen matrix.

Cook

The Examiner argues that Cook's composite of insoluble collagen and OP "had the consistency of wet sand, which was spooned into the segmental defect site.. . . . It would have been obvious . . . to add a gelling agent, such as CMC, because it [sic] the implant could be molded into the desired shape or formulated for injection." Office Action, p. 7, line 18 through p. 8, line 3. Applicants respectfully disagree.

First, Cook does not teach that the "wet sand" consistency is disadvantageous and therefore the use of a binding agent is desirable. It does not teach or even suggest that a problem exists with the consistency or handling characteristics of this composition. The "wet sand" composition can certainly be molded into various shapes to fill in a bone defect, even without the presence of a binding agent. Thus, like Doll, Cook does not provide any motivation to use a binding agent comprising cellulose, dextran, white petrolatum, or a derivative thereof in its composite.

Second, contrary to the Examiner's assertion, a person of ordinary skill in the art would not have wanted to add CMC to Cook's composite, which contains collagen. As discussed above, a person of ordinary skill in the art knew at the time of the invention that collagen and CMC were incompatible in pharmaceutical compositions.

[redacted]

Nunez

This reference discloses the use of tissue sealants such as fibrin glue. In this reference, tissue sealants refer to compositions containing plasma proteins. See, e.g., p. 6, line 1. Claim 1 as amended recites a binding agent selected from the group consisting of mannitol, cellulose, dextran, white petrolatum and derivatives thereof. None of these binding agents contains plasma proteins. Thus, these binding agents are not tissue sealants contemplated by Nunez.

Further, Nunez calls for the use of demineralized bone matrix (DBM). However, DBM is expressly excluded in claim 1. Nunez does not provide any motivation to use a matrix material that does not comprise DBM. The Examiner is mistaken when he states that collagen provides a more permissive surface for cell attachment. The observation that collagen was superior for cell attachment was made by comparing collagen with hydroxyapatite (HA), not with DBM. See Doll. Neither Doll nor Nunez states that collagen is more permissive for cell attachment than DBM.

Alberts and Reddi

According to the Examiner, Alberts teaches the physiological properties of the extracellular matrix (ECM), and Reddi teaches that biomaterials mimic the ECM; and it would have been obvious to mimic the ECM in order to achieve osteoinduction and to mimic a gel-like "ground" substance with a gel forming material such as CMC. Office Action, p. 8, lines 10-14.

Applicants respectfully submit that there is a huge leap of logic in the Examiner's argument. It is obvious that not all "gel forming" substances mimic the ECM. And neither Alberts nor Reddi teaches or suggests that mannitol, cellulose, dextran and white petrolatum mimic the ECM.

In conclusion, Sato, Wozney, Doll, Cook, Nunez, Ammann, Alberts, and Reddi, alone or in combination, do not provide a person of ordinary skill in the art with any teachings or motivations to arrive at a tissue-inductive device containing (1) a purified osteogenic protein that is not associated with other osteogenic proteins with which it is normally associated *in vivo*; (2) a matrix that does not comprise a synthetic polymer or DBM; and (3) a binding agent selected from the group consisting of cellulose, dextran, white petrolatum, and derivatives thereof. In short, the Examiner has not established a *prima facie* case of obviousness in regard to claims 1, 13, 17-25 and 31.

V

Claims 1 and 6 remain rejected as allegedly obvious over Sato in view of Ogawa. The Examiner argues that the feature relied upon by applicants in their previous Response, i.e., the meaning of "purified," is not recited in the claim. Office Action, p. 8, ¶ 11.

In light of this comment, applicants have amended claim 1 to include this feature (Amendment 1, *supra*). Claim 1 and dependent claim 6 would thus be distinguishable over the cited art.

Regarding claim 6, the Examiner also argues, apparently based on Ogawa, that it would have been obvious at the time of the invention to use TGF-β and BMP in the device of claim 1. Applicants respectfully point out that claim 6 calls for the use of two or more different "osteogenic protein[s] capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects" (claim 1). However, TGF-β is not such an osteogenic protein, as applicants explained in their January 27, 1999 *Preliminary Amendment and Response*. See, e.g., p. 6 of that document.

VI

Claims 1 and 14 stand rejected as allegedly obvious over Kuberasampath or Sato in view of Wozney and Ammann as applied to claims 1 and 13 above, and further in view of a FMC publication.

As discussed above, claims 1 and 14 as amended are distinguishable over the combination of Kuberasampath, Wozney and Ammann (Section II, *supra*) and over the combination of Sato and Ammann (Section III, *supra*). The FMC publication describes only the biophysical properties of FMC' cellulose and CMC products. The publication does not remedy the deficiencies of the other cited art. Thus, the instant rejection should be withdrawn.

CONCLUSION

Applicants submit that the grounds for rejection asserted by the Examiner would be overcome by the preliminary amendments applicants set forth above. And these

[redacted]

amendments would not introduce any new matter or raise any new issues that would require further searches.

On this basis, applicants respectfully submit that entry of the proposed amendments is proper, and early favorable action is solicited.

Respectfully submitted,

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Appendix

1. (Five Times Amended) A device for inducing local bone or cartilage formation, comprising:

a purified osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects, said purified osteogenic protein being not associated with other osteogenic proteins with which it is normally associated *in vivo*;

a matrix [other than] that does not comprise a synthetic polymer or demineralized bone; and

a binding agent selected from the group consisting of mannitol, dextran, cellulose, white petrolatum, and derivatives thereof.

2. (Thrice Amended) The device of claim 1, wherein said osteogenic protein is selected from the group consisting of: OP1, OP2, OP3, BMP2, BMP3, BMP4, BMP5, BMP6, BMP9, BMP10, BMP11, BMP12, BMP15, BMP16, DPP, Vgl, 60A protein, GDF-1, GDF3, GDF5, GDF6, GDF7, GDF8, GDF9, GDF10, GDF11, and [conservative amino acid sequence] variants thereof having conservative amino acid substitutions and substantially similar osteogenic activity.

3. (Thrice Amended) The device of claim 1, wherein said osteogenic

protein is selected from the group consisting of OP1, OP2, BMP2, BMP4, BMP5, BMP6, and [conservative amino acid sequence] variants thereof having conservative amino acid substitutions and substantially similar osteogenic activity.

Delete claim 10 without prejudice.

17. (Twice Amended) A device for inducing local bone or cartilage formation, comprising at least approximately 1.25 mg of purified OP-1 and at least approximately 180 mg of carboxymethylcellulose per 1000mg of collagen matrix, wherein said purified OP-1 is not associated with other osteogenic proteins with which it is normally associated *in vivo*.

20. (Four Times Amended) A device for inducing local cartilage or bone formation comprising a purified osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects and a carrier, wherein said carrier comprises one part binding agent and 10 or fewer parts (w/w) matrix, and said purified osteogenic protein is not associated with other osteogenic proteins with which it is normally associated *in vivo*.

23. (Four Times Amended) A device for inducing local bone or cartilage formation comprising a purified osteogenic protein capable of inducing repair of

[redacted]

endochondral bone, or cartilage, chondral, or osteochondral defects and a carrier, wherein said carrier comprises 10 or fewer parts (w/w) binding agent and 1 part matrix, and said purified osteogenic protein is not associated with other osteogenic proteins with which it is normally associated *in vivo*.

31. (Amended) A device for inducing local bone or cartilage formation comprising:

purified [osteogenic protein] OP-1;

collagen matrix; and

carboxymethylcellulose;

wherein said purified OP-1 is not associated with other osteogenic proteins with which it is normally associated *in vivo*.

32. (Amended) A kit for inducing local bone or cartilage formation using the device of claim 1, the kit comprising:

(a) a receptacle adapted to house [an] the osteogenic protein and [a] the matrix material, and

(b) a receptacle adapted to house [a] the binding agent,

wherein the osteogenic protein and matrix material are provided in the receptacle of part (a), and the binding agent is provided in the receptacle of part (b).

[redacted]

35. (Amended) A kit for inducing local bone or cartilage formation using the device of claim 1, the kit comprising:

a first receptacle adapted to house [an] the osteogenic protein, [a] the matrix material, and [a] the binding agent,

wherein the osteogenic protein, matrix material and binding agent are provided in said receptacle.